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Diagnostic Accuracy of Statistical Pattern Recognition of Electroencephalogram Registration in Evaluation of Cognitive Impairment and Dementia

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Key Words
Alzheimer's disease · Vascular dementia · Lewy body dementia · Parkinson's disease dementia · Depression · Frontal lobe dementia · Mild cognitive impairment · Sensitivity · Specificity

Abstract
Background: There is still a need for simple, noninvasive, and inexpensive methods to diagnose the causes of cognitive impairment and dementia. In this study, contemporary statistical methods were used to classify the clinical cases of cognitive impairment based on electroencephalograms (EEG). ***Methods:*** An EEG database was established from seven different groups of subjects with cognitive impairment and dementia as well as healthy controls. A classifier was created for each possible pair of groups using statistical pattern recognition (SPR). ***Results:*** A good-to-excellent separation was found when differentiating cases of degenerative disorders from controls, vascular disorders, and depression but this was less so when the likelihood of comorbidity was high. ***Conclusions:*** Using EEG with SPR seems to be a reliable method for diagnosing the causes of cognitive impairment and dementia, but comorbidity must be taken into account.
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Introduction

It is estimated that as many as 10% of those aged over 65 years are affected with dementia. One of the main tasks in the diagnostic work-up of dementia is to differentiate between the various causes, but the current criteria for diagnosis of the most prevalent forms of dementia are of varying accuracy and up to 10% of cases of dementia are difficult to diagnose with reasonable confidence [1].

Alzheimer's disease (AD) is the most common neurodegenerative disease causing cognitive impairment and dementia, with more than 20 million cases worldwide [2]. In the clinical setting the clinical diagnosis of AD is made according to DSM IV criteria or the ICD 10. According to both criteria the diagnosis includes a two-step approach with the initial recognition of dementia defined by impairment of activities of daily living caused by cognitive decline in more than one domain, memory being one of them. The second step is to identify the clinical features of AD. According to these criteria, AD is not diagnosed until the disease has caused dementia, but it is now recognized that in most cases it takes several years to develop the disease to the extent that it fulfills the criteria of dementia. The same is the case for the research criteria of NINCDS/ADRDA [3]. According to these

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criteria, the AD phenotype is described in exclusionary terms. Two consensus papers by Dubois et al. [4, 5] have challenged that approach. The authors propose that the research criteria of AD should be based on impairment of episodic memory in addition to positive biological markers, but dementia is not essential for the diagnosis [4, 5]. This new approach will most likely form the basis of further research using biological markers to identify the disease in the predementia stage or prodromal AD, a term proposed by Dubois et al. [5].

Many terms have been used to describe the predementia stage but the most prevalent is mild cognitive impairment (MCI) [6, 7]. In clinical research this term is used to describe subjects that experience cognitive impairment that is verified by a relative, most often including memory impairment, but the symptoms are of insufficient severity to warrant the diagnosis of dementia. It is widely accepted that there are two major forms of MCI, amnestic and nonamnestic, which are sometimes divided further into single or multiple cognitive domain impairments [8]. The risk of an MCI patient converting to dementia has been estimated between 6 and 15% per year [9] but many individuals remain stable and never develop dementia. It is important to characterize those MCI subjects subsequently progressing to AD in order to intervene early without treating non-AD individuals.

Most of the methods proposed for characterizing biological markers of AD are complicated and expensive [5], e.g. quantification of the medial temporal lobe structures via magnetic resonance imaging (MRI) and positron emission tomography (PET) with fluorodeoxyglucose, a method that has been approved by the FDA in the USA for diagnostic purposes as it is sensitive and specific in the detection of early AD [10]. The third method is invasive as it is analysis of cerebrospinal fluid of beta amyloid and tau proteins. These methods have shown promising results in evaluating MCI patients and in differentiating those that progress to AD from those that remain stable [11–13]. None of these methods are used frequently outside academic memory clinics. There is therefore still a need for methods using biological criteria of early AD that are accessible and simple and that can be applied more widely than the aforementioned methods.

As AD is a disorder of the brain cortex and electroencephalograms (EEG) reflect cortical activity, it is reasonable that such a method could show derangement in cortical function. The method is noninvasive, inexpensive, and simple to use and can thus be applied outside the main centers. The main EEG abnormalities in AD are a slowing and decrease in alpha activity with a corresponding increase in theta and delta activities [14]. These abnormalities have been shown to correlate with the severity of the disease [15]. By using computerized spectral analysis of EEG rather than visual analysis, quantitative data is gained. Using different methods of analysis it has been estimated that the diagnostic accuracy of spectral and visual EEG analysis is approximately 80%, with good sensitivity but poor specificity [16, 17]. These results have therefore not convinced clinicians to use EEG routinely in the diagnostic work-up of dementia. However, recent studies have demonstrated the usefulness of EEG in differentiating AD from some other important causes of dementia, by applying contemporary statistical methods to the analysis of quantitative EEG (qEEG), i.e. dementia of the Lewy body type (DLB) and Parkinson's disease dementia (PDD) [18], frontal lobe dementia (FLD) [19], and subcortical vascular dementia (subcortical VaD) [20]. Furthermore, depression (DPR) can mimic mild dementia. Emotion-related disturbances, such as DPR and anxiety, have been linked to relative right-sided resting frontal EEG asymmetry in adults [21].

The objective of this study is to propose a multivariate differential diagnosis approach and evaluate whether this qEEG methodology can contribute significantly to a typical diagnostic work-up of cognitive impairment and dementia.

Materials and Methods

Participants

Clinical cases were participants recruited in the Memory Clinic of the Geriatric Department, National University Hospital, Reykjavik, Iceland, diagnosed using a standard procedure consisting of clinical information, biochemistry, morphologic methods (CT scan or MRI), neuropsychological evaluation, and isotope scanning (SPECT). In many cases of suspected DLB, a scan using a radioactive isotope with high affinity for dopamine neurones in the brain, ioflupane (^{123}I), was performed (DaTSCAN®). In a few instances liquor analysis of beta amyloid, total tau protein, and phosphorylated tau protein was performed.

The patients had earlier been diagnosed after a visit to the Memory Clinic but that information was not used for this project as the diagnosis was recorded according to the ICD-10 and there can be some inconsistency in diagnosis between various doctors. Therefore, each patient's diagnosis was re-evaluated independently by two clinicians on the basis of all available information in the patient records apart from any information on EEG. The diagnosis was made according to NINCDS-ADRDA criteria [3] regarding AD and according to NINDS-AIREN criteria [22] regarding vascular dementia, and regarding Lewy

Table 1. Composition of groups used in the construction of the classifiers presented in this article

	n	Age, years
NRM	226	65±9
AD	239	78±6
VaD	58	78±7
sMCI	41	73±8
DLBP	52	76±7
FLD	14	73±10
DPR	24	75±7
Total	654	70±8

The description of each group is in the text of the article. Ages are presented as means ± SD of the age distribution.

body dementia the consensus criteria of McKeith et al. [23] were used. For FLD, the criteria of Neary et al. [24] were used. When these independent diagnoses were inconsistent in any way, a consensus diagnosis was made with the participation of a third clinician not otherwise involved in the study. All of the participants were living in their homes at the time of EEG registration but some of them were attending a day care center. The extent of their cognitive impairment ranged from MCI to moderately severe dementia.

Parallel to EEG registration, all participants were evaluated using the mini mental state examination (MMSE) [25] and the digit symbol substitution test (DSST) [26]. No patient was excluded from the study if an EEG registration had been successfully performed.

The participants in the control group were distributed in age between 50 and 90 years (table 1). They were recruited via TV advertisements and in service centers for senior citizens but some of them were relatives of a patient. Each individual in the control group gave information, if relevant, on their history of head injury with loss of consciousness, neurological diseases such as Parkinson's and MS, addiction to alcohol or drugs, and any major medical condition. In addition to MMSE and DSST the control subjects were evaluated using the geriatric depression scale, a 15-item list [27]. The MMSE scores of the 226 control subjects were distributed as follows (MMSE score/n): 30/100, 29/73, 28/39, 27/10, and 26/4. This indicates that the control group is not an unrepresentative very healthy cohort.

The participants were placed in one of the following 7 groups (table 1): (1) healthy controls (NRM), (2) AD with an MMSE score higher than 23, (3) VaD, (4) MCI stable for more than 24 months (sMCI), (5) DLB and PDD, (6) FLD, and (7) DPR. It has been argued that DLB and PDD are essentially the same disorder with different clinical manifestations [28], and as these two groups were rather small they were combined in our analysis. This combined group was labeled DLBP. For this analysis, a total of 654 EEG registrations were used.

The study was performed according to Good Clinical Practice requirements and it was approved by the Icelandic National Bioethics Committee (reference No. 04-130). All participants signed a written informed consent form prior to participation.

qEEG Registration

The EEG was recorded for 3 min during which the subjects were at rest with their eyes closed. The IS 10–20 system was used for electrode placement. The following 19 electrodes were used: Fp1, Fp2, F3, F4, F7, F8, Fz, T3, T4, T5, T6, C3, C4, Cz, P3, P4, Pz, O1, and O2. The average potential was used as a reference. Two bipolar electro-oculography channels and one electrocardiogram were applied to monitor artifacts. The subjects were alerted if they became visibly drowsy.

The EEGs were recorded using NicoletOne EEG Systems from CareFusion*. Subsequent analysis was done in the Matlab environment from MathWorks*.

qEEG Data Analysis

A classifier was created for each possible pair of groups using statistical pattern recognition (SPR). The idea is that using the resulting 21 classifiers it is possible, based on a qEEG measurement from an individual visiting a memory clinic, to determine which of the 7 groups the corresponding individual most likely belongs to.

For each EEG measurement 20 spectral features are extracted, as well as 37 coherence features for each of the said spectral features. Thus a total of 1,120 features are extracted from each EEG recording. The reliability of the EEG features used in this study has already been investigated [29]. A brief description of those features is given in table 2.

The data was analyzed applying an SPR technique which is used to construct a classifier from two groups of qEEGs, e.g. qEEGs from groups A and B [30]. When an EEG is classified the classifier returns an index, i.e. A-B index, with a value between 0 and 1. If the A-B index is close to 0 the EEG is indistinguishable from the EEGs in group A and if the A-B index is close to 1 the EEG is indistinguishable from the EEGs in group B. Twenty-one classifiers were constructed from the 7 groups in the study, and the identifiers of the classifiers are shown in table 3. Each classifier relies on a set of 20 qEEG features out of the 1,120 available features. For each classifier construction there are therefore 3×10^{42} distinct possibilities. A genetic algorithm [31] was applied to select the features used in the construction of the classifier for each pair of groups. The target value of the genetic evolution of classifiers was the area under curve (AUC) of the corresponding receiver operating characteristic (ROC) curve. The AUC represents the quality of the classifier; if the AUC = 0.5 the classification is random and if the AUC = 1 then the classification is perfect. The objective was not to find the best classifier in each case, which is a near impossible task, but rather to find a classifier with clinically acceptable qualities.

A 10-fold cross-validation approach is used to obtain average values for accuracy, sensitivity, and specificity for each classifier [32]. The standard deviations of those are estimated using the bootstrap approach [33].

Table 2. EEG features used for the classifiers

Spectral feature	Description
1	Power in the δ frequency band (0.5–3.5 Hz)
2	Power in the θ frequency band (3.5–7.5 Hz)
3	Power in the α_1 frequency band (7.5–9.5 Hz)
4	Power in the α_2 frequency band (9.5–12.5 Hz)
5	Power in the β_1 frequency band (12.5–17.5 Hz)
6	Power in the β_2 frequency band (17.5–25 Hz)
7	Power in the γ frequency band (25–40 Hz)
8	Relative power in the δ frequency band
9	Relative power in the θ frequency band
10	Relative power in the α_1 frequency band
11	Relative power in the α_2 frequency band
12	Relative power in the β_1 frequency band
13	Relative power in the β_2 frequency band
14	Relative power in the γ frequency band
15	Total power of the EEG power spectrum (0.5–40 Hz)
16	Peak α frequency
17	Power ratio: $R_1 = \theta / (\alpha_1 + \alpha_2 + \beta_1)$
18	Power ratio: $R_2 = (\delta + \theta) / (\alpha_1 + \alpha_2 + \beta_1 + \beta_2)$
19	Power ratio: $R_3 = \theta / (\alpha_1 + \alpha_2)$
20	Power ratio: $R_4 = \theta / (\beta_1 + \beta_2)$
Coherences evaluated for each spectral feature	
	Far intrahemispheric
1–10	Fp1/O1, Fp2/O2, Fp1/P3, Fp2/P4, F3/O1, F4/O2, F3/P3, F4/P4, C3/O1, C4/O2
	Far interhemispheric
11–17	F7/F8, F3/F4, T3/T4, C3/C4, T5/T6, P3/P4, O1/O2
	Local anterior
18–27	Fp1/F7, Fp2/F8, Fp1/F3, Fp2/F4, F7/C3, F8/C4, F7/T3, F8/T4, F3/C3, F4/C4
	Local posterior
28–37	T5/O1, T6/O2, P3/O1, P4/O2, C3/T5, C4/T6, P3/C3, P4/C4 , P3/T5, P4/T6

Table 3. AUC (accuracy; sensitivity/specificity) and nomenclature of classifiers and groups. The accuracy, sensitivity, and specificity is based on a decision point at an index value equal to 0.5 for each classifier and evaluated using 10-fold cross-validation

	NRM	AD	VaD	sMCI	DLBP	FLD	DPR
NRM		93 (86; 83/88)	93 (86; 86/86)	87 (80; 80/80)	99 (97; 98/95)	92 (87; 92/82)	89 (83; 82/85)
AD	NRM-AD		80 (75; 77/71)	88 (80; 75/83)	97 (91; 93/86)	93 (88; 82/93)	79 (73; 66/75)
VaD	NRM-VaD	AD-VaD		89 (84; 91/78)	94 (87; 88/87)	87 (80; 74/87)	86 (78; 84/72)
sMCI	NRM-sMCI	AD-sMCI	VaD-sMCI		98 (95; 93/96)	93 (83; 87/80)	85 (78; 76/80)
DLBP	NRM-DLBP	AD-DLBP	VaD-DLBP	sMCI-DLBP		96 (93; 98/89)	98 (93; 92/94)
FLD	NRM-FLD	AD-FLD	VaD-FLD	sMCI-FLD	DLBP-FLD		86 (86; 88/84)
DPR	NRM-DPR	AD-DPR	VaD-DPR	sMCI-DPR	DLBP-DPR	FLD-DPR	

All numbers are percentages.

Results

The 21 classifiers presented in this article and their corresponding AUCs, accuracies, sensitivities, and specificities are listed in table 3. The uncertainties in those values are smaller than 1%. The corresponding ROC curves and index distributions as a result of the 10-fold cross-validations are shown for 2 chosen cases in figures 1 and 2.

Figure 1 shows the ROC curve corresponding to the optimum set of features as determined by the evolution-

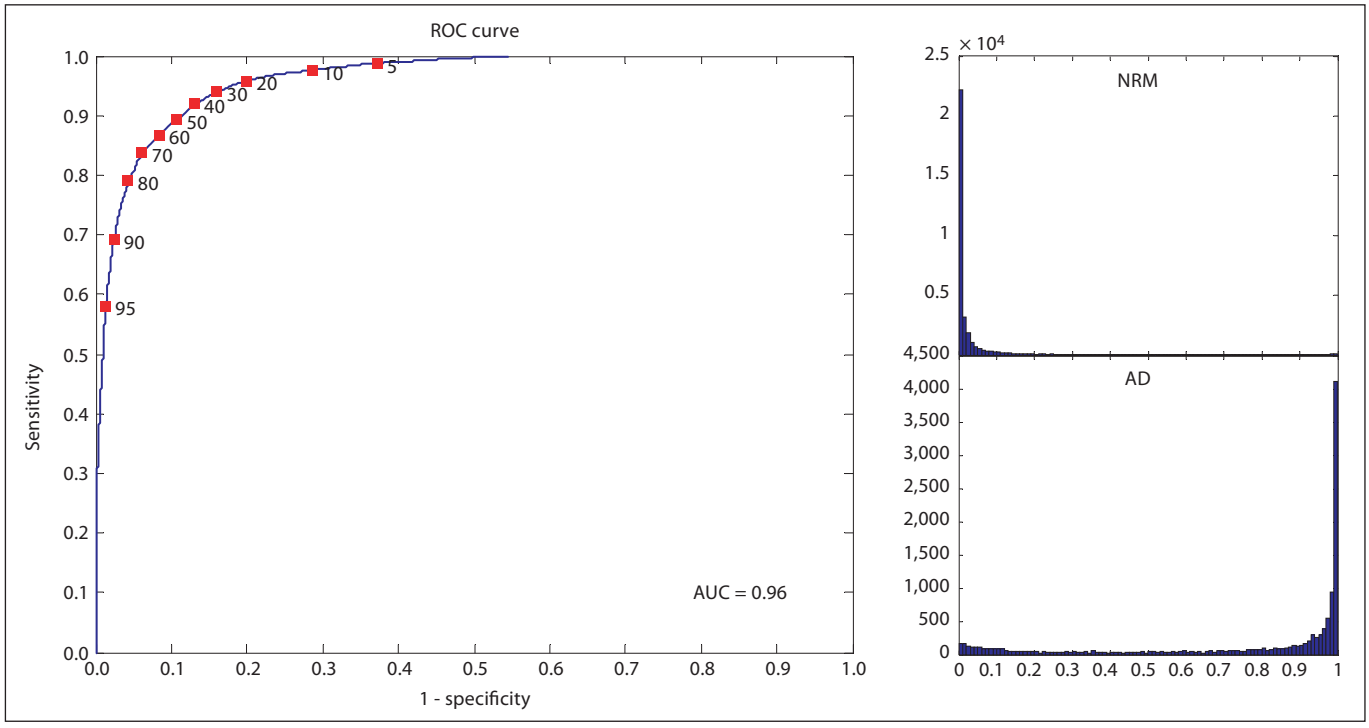

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Fig. 1. ROC curve for the NRM-AD classifier. The small frames show the distributions of classification indices resulting from a 10-fold cross-validation for each of the two groups NRM and AD. The accuracy, sensitivity, and specificity of the classifier are listed in table 3.

ary algorithm for the NRM-AD classifier. The value of the AUC for this classifier is an average of 100 times 10-fold cross-validations. During each cross-validation, 10% of each group is classified and assigned an index ranging from 0 to 1. The small frames in figure 1 show the distributions of indices generated by the 100 instances of the 10-fold cross-validation separately for the groups NRM and AD. This example shows two groups which have very different characteristics based on their collective EEGs; it is evident from the distribution of indices and that the accuracy is 86%.

This is not true for all of the classifiers, and as an example the ROC curve and the corresponding histograms of indices for the AD-VaD classifier are shown in figure 2. In this case the accuracy is 75% and the distributions of indices as a result of the cross-validations are shown in the small frames. Here the distributions overlap considerably indicating that the VaD group is heterogeneous. This figure will be discussed further in the next section.

When an evolutionary algorithm approach is used to search for a suitable set of 20 EEG features, for a given classifier, the result is a large number of sets of nearly equal quality. Analyzing the incidence frequency of each feature in the genetic evolutionary process, it is possible to estimate the relevance of each feature. The outcome is not unique; different evolutionary runs may result in different sets of features that complement each other well. The 5 most relevant features for each classifier are presented in table 4.

Discussion

The diagnoses of AD and other causes of cognitive impairment and dementia are based on clinical signs and symptoms in addition to physiological procedures evaluating biological markers for those diseases. It has, however, been difficult to diagnose the various causes of cognitive decline in the prodromal stage of dementia, classically defined as MCI. In recent years, a great deal of progress has been made in validating the use of various biological markers, primarily of AD. These biomarkers have shown good sensitivity and specificity and recently they have been proposed as background for research

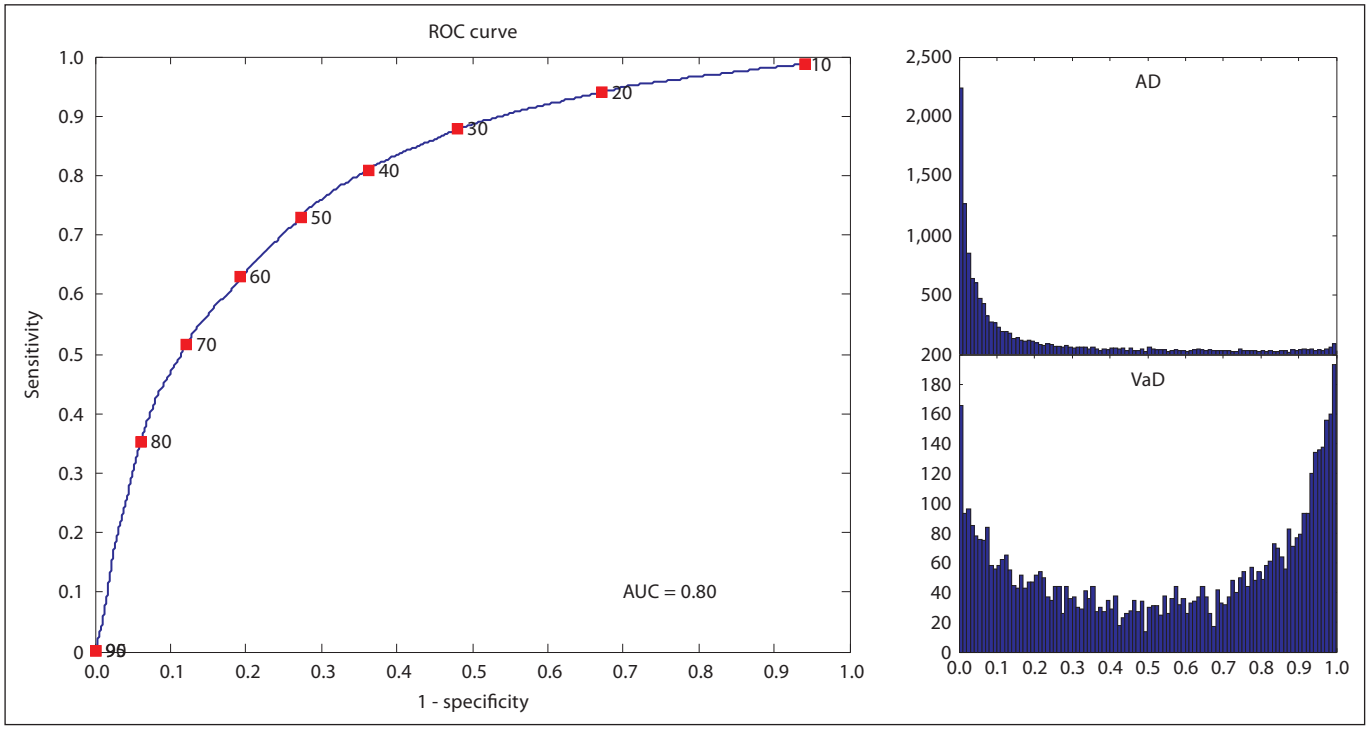

Fig. 2. ROC curve for the AD-VaD classifier. The small frames show the distributions of classification indices resulting from a 10-fold cross-validation for each of the two groups AD and VaD. The accuracy, sensitivity, and specificity of the classifier are listed in table 3.

criteria of AD [5]. The methods are, however, complex, expensive, and to some extent invasive and will not be generally used outside the academic memory clinic. There is therefore still a need for generally applicable, simple, and reliable methods for quantification of biological markers for these diseases, not least in the earliest phases.

In this study, a conventional EEG registration was performed on patients referred to a memory clinic as well as on a number of healthy individuals living in the community (altogether over 650 registrations, see table 1). The features extracted from the registrations were analyzed using SPR and without a pre-emptive idea of any EEG derangement. This is one of the methods of bioinformatics used when analyzing a vast amount of information. The primary goal of bioinformatics is to increase the understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques such as pattern recognition as used in this project, data mining, and machine learning algorithms to achieve this goal [34]. By using SPR classifiers to separate the various groups in a pair-wise manner (altogether 21 classifiers), a good-to-excellent result was achieved depending on the groups being separated. When an EEG is classified using the 21 classifiers, each classifier returns an index from 0 to 1.

When using the SPR classifier to separate groups that are rarely clinically overlapping such as NRM versus AD or AD versus DLBP, the separation was in excess of 85%. On the other hand, when the classifier was used to separate groups that might be overlapping such as AD versus VaD, the separation was not as good, most likely due to the contribution of both diseases (mixed AD or AD with cerebrovascular changes). The same was the case in separation of DPR versus AD or DPR versus VaD, most likely indicating comorbidity (table 3). This is in line with the results of other groups using the same technique on patients with AD but using pre-emptive EEG features known to be deranged in this disease [35].

A precursor of the method presented here was used in a study conducted at a memory clinic [36]. The authors, however, only used one dimension of the method (NRM vs. AD), when in reality the patients had different causes

Table 4. Most relevant EEG features for each of the 21 classifiers. The description of the features can be found in table 2

Classifier	Feature 1	Feature 2	Feature 3	Feature 4	Feature 5
NRM-AD	O2–θ	T3–rβ_1	Cz–θ	O1/O2–β_1	T6/O2–paf
NRM-VaD	F7/T3–β_2	F4/C4–β_1	C4/T6–γ	T6–R_1	Fp2/F8–R_3
NRM-sMCI	T5/T6–θ	P4–β_1	O1/O2–θ	T6/O2–R_2	Fz–θ
NRM-DLBP	T5/T6–rδ	P4–α_1	T5–γ	T6/O2–rθ	P3/P4–α_2
NRM-FLD	Fp2/F8–paf	F3/C3–R_4	F3/O1–R_3	T5/T6–rθ	Fp1/F7–θ
NRM-DPR	P4/O2–rδ	C4/T6–θ	Fp2/O2–β_2	Cz–γ	C3/O1–γ
AD-VaD	T5/T6–rδ	T4–R_4	Pz–δ	F3/F4–paf	F4/P4–γ
AD-sMCI	F7/T3–δ	P4/C4–α_1	T3–α_1	F4/P4–rα_1	P3/T5–δ
AD-DLBP	C3/C4–α_2	Fp1/F3–paf	F8/T4–α_2	T5/T6–rθ	Fp2/F8–β_1
AD-FLD	Fp2–α_1	F8–β_1	F8/C4–δ	P4/T6–R_2	C4/T6–R_4
AD-DPR	Cz–γ	Fp1–α_1	Fp2–rβ_2	C4–rα_1	F3/F4–rα_2
VaD-sMCI	P4/T6–tp	T6/O2–R_3	T5/O1–tp	P4/C4–tp	P4–rγ
VaD-DLBP	Fz–rβ_1	Fp1/F3–rα_2	Pz–α_2	F8–rα_1	F7/C3–α_2
VaD-FLD	T3/T4–δ	T5–γ	T5/T6–α_1	F7/C3–δ	Fz–rα_1
VaD-DPR	Fp2–γ	F8/C4–α_1	C3/T5–α_2	F3/F4–α_2	Fp2/O2–θ
sMCI-DLBP	T6–γ	C4/O2–α_2	F7–tp	O2–rβ_2	P3–rβ_1
sMCI-FLD	F7/T3–paf	Fp1/O1–α_1	F7/F8–paf	C3/O1–rβ_2	Fp1/F3–rβ_1
sMCI-DPR	T3/T4–rδ	T3/T4–rβ_2	F8/C4–paf	F7–α_1	T4–rβ_2
DLBP-FLD	T5–β_1	O1/O2–δ	P3/O1–γ	O2–rδ	P4–α_1
DLBP-DPR	Fp2/O2–α_2	C4/T6–α_2	Fp2–R_1	F3/C3–rγ	P3/O1–δ
FLD-DPR	P4–rβ_2	Fz–rα_2	Fp1/F3–α_1	C4/T6–γ	C4–tp

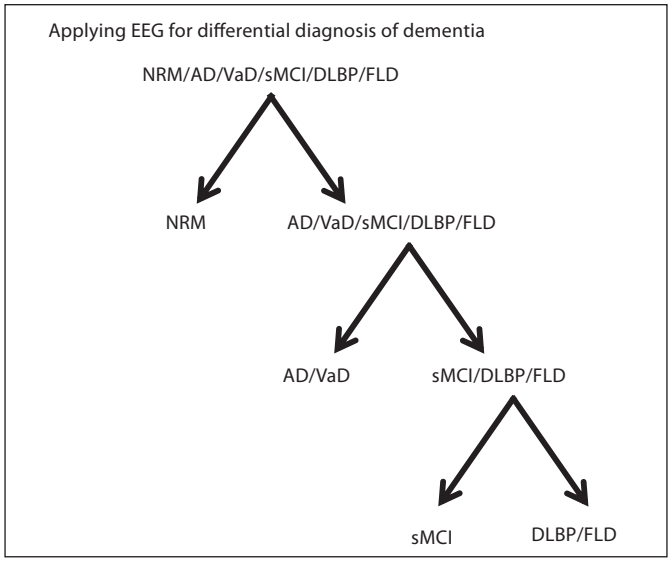

Fig. 3. A stepwise procedure which may be applied to using the 21 qEEG classifiers presented in this paper for differential diagnosis of dementia. The presence of depression is checked at the end of each step using the corresponding X-DPR classifier.

of cognitive impairment and dementia demonstrating the need for multiple comparisons.

The clinical diagnosis of AD does not correlate very well with neuropathology, not least in the oldest individuals [37]. This is most probably the reason a minor fraction of those diagnosed with AD have EEG features of normal individuals as seen in figure 1.

The AD group only contained patients with mild AD having an MMSE score of 24 or more, not excluding mixed AD or AD with cerebrovascular changes. This is by far the biggest group of patients receiving dementia diagnosis in a memory clinic.

Patients referred to a memory clinic who are diagnosed with MCI constitute a heterogeneous group. Some will remain stable while others are in a prodromal stage of dementia (most often AD). In this study many subjects in the MCI group showed EEG characteristics similar to those of AD subjects, indicating that many of the MCI subjects actually were in the prodromal stage of AD. The MCI group was divided into two groups: one of patients progressing to dementia and the other of patients who remained stable for 2 years or more. The separation of AD and stable MCI was 80%, which is 10% less than the separation achieved for NRM versus AD, suggesting that

some of the subjects in the stable MCI group could still progress to AD in spite of being stable for 2 years. Further discussion related to the MCI group, especially progressive MCI, is beyond the scope of this work.

The separation of AD from DLBP and FLD was excellent (91 and 88%, respectively). These disorders have a different pathology and topography in the brain and the clinical signs are different when the diseases have progressed to dementia, but in the earliest phases it can be difficult to differentiate between them based only on the clinical signs.

Vascular dementia is primarily diagnosed by clinical signs and symptoms and by morphologic neuroradiology. In this study, the separation of VaD by SPR analysis of EEG was, as anticipated, less than that of AD from other causes of cognitive impairment; however, separation of VaD from NRM individuals was fairly good or little less than 90%. The separation of VaD and DPR was less than or around 75%, most likely due to comorbidity.

It is of interest to see that the separation of the combined group, DLBP, from all other groups is excellent or 87–97%. The clinical diagnosis of DLB is difficult in the earliest phases and there are few biological markers to rely on apart from the scintigram SPECT with cocaine analog (e.g. DaTSCAN^{TM}). The EEG technique presented here can therefore be a valuable tool for clinicians in separating DLBP from other causes when symptoms are subtle. Another study reported AUC values of 0.75–0.80 and 0.91–0.97 for AD-DLB and NRM-DLB, respectively [38]. The main EEG features separating the DLB group from AD and NRM were found to be greater variability in delta band power in parietal electrodes, a higher degree of overall coherence in the delta band, and a lower degree of overall coherence in the alpha band. Two of the top five EEG features in the NRM-DLBP classifier are related to coherence in the alpha and delta bands and two of the top five features in the AD-DLBP are related to coherence in the alpha band (see table 4). The corresponding AUC values in table 3 are 0.99 and 0.97 for the NRM-DLBP and AD-DLBP classifiers, respectively. The separation of the AD and DLBP groups in the present study was considerably higher. This could be due to one or more of the following reasons: (1) the AD group used here was larger, (2) 20 EEG features were used in the classifier instead of 4 [38], and (3) in the present study the DLB and PDD groups were combined.

The group with FLD turned out to be distinct, and separation from all other groups was strong. However, the group is small, which makes it hard to come to any firm conclusion about the bounds of the properties of the classifiers involving FLD. This group is heterogeneous pathologically and this is reflected by the EEG as well. With respect to clinical applicability it could be of interest to be able to subdivide further with a bigger group.

Depression can mask cognitive impairment and even mild dementia. It is also an important comorbidity of patients with organic dementia, not least AD and VaD. The present EEG method showed a modest separation of depression from both AD and VaD indicating comorbidity. The separation from other groups was better, and of special interest is the separation from the NRM group of 85% indicating physiological changes associated with depression. It has to be kept in mind that in this study, the group with depression consisted of individuals seeking a memory clinic for cognitive impairment. Causes of an organic nature were ruled out and the diagnosis depended on clinical signs of depression. It cannot be ruled out that at least some of the individuals had depression as an early sign of dementia and the group is most likely not representative of typical depression. It is, however, important to keep in mind that these are typically patients that need to be differentiated from organic causes of cognitive impairment. This method can therefore be helpful in the setting of a memory clinic, but the value of the method in other groups of depressive patients cannot be confirmed in this study.

The strength of this method is that it was evaluated in everyday practice in a memory clinic with almost no exclusion of subjects other than those few who rejected participation. It thus reflects the real-life situation in such a setting. Another methodological strength is the number of registrations of the most prevalent groups, making the statistical analysis robust. The weakness of this study is the low numbers of individuals in some of the groups making the results less reliable in those cases. Furthermore, it cannot be ruled out that by combining individuals with DLB and PDD into one group, i.e. DLPB, the specific features of each of the groups could be masked. Even though the MCI patients were followed for at least 2 years, the other clinical groups were diagnosed cross-sectionally and therefore mistakes in diagnosis cannot be ruled out. The methods used in the diagnostic work-up are similar to those used in most other memory clinics, it is likely that the proportion of incorrect diagnoses is of a similar magnitude as in other clinics or 5–15% [37].

Taking these strengths and weaknesses into consideration, EEG registration with SPR analysis seems to be a simple, inexpensive, and reasonably robust method for separating the various groups of patients that are referred

to a memory clinic. The clinician needs to take into account the comorbidity that exists in some patients and the possible mixture of disorders that might be relevant. This is a method that could be an indicator of a biological marker and as such could be a valuable tool to come to a conclusion in the diagnostic process. Furthermore, as the technical process is simple, this method can be helpful in the general practitioner's office for the decision of referral as well as for a final work-up in a memory clinic. These results need to be confirmed in other independent studies.

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